Stereoselective Synthesis of L-Amino Acids via Strecker and Ugi Reaktions on Carbohydrate Templates

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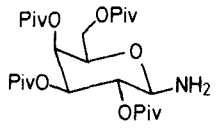
Dedicated to Professor Leopold Horner on the occasion of his 80th birthday

L-Amino acid derivatives are stereoselectively synthesized in high yield using 2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosylamine or 2,3,4-tri-*O*-pivaloyl-β-L-fucopyranosylamine as the chiral auxiliary in Strecker and Ugi reactions.

The L-amino acids are not only of great interest as the constituents of natural proteins and components of numerous antibiotics. Unnatural L-amino acids also receive increasing attention as starting materials for syntheses of peptidomimetics or drugs with non-peptide structure.[1,2] Recently, we reported on stereoselective syntheses of D-amino acids via Lewis acid-catalyzed Strecker[3,4] and Ugi reactions[5,6] in which 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine (**1**) was used as the stereodifferentiating auxiliary. While the direction of asymmetric induction of the Strecker process can be reversed by changing the solvent from 2-propanol to chloroform,[7] the more efficient Ugi reaction does not show this interesting and useful effect. In order to achieve an efficient stereodifferentiation in both, the Strecker and Ugi syntheses of L-amino acid precursors, we have developed the 2,3,4-tri-*O*-pivaloyl-α-D-arabinosylamine (**2**) as a new chiral auxiliary.[8] Although the arabinosylamine **2** belongs to the stereochemical D-series, it is almost a mirror image of the D-galactosylamine **1**. A further formal enantiomer of **1** is the L-fucosylamine **3** derived from the likewise natural, but more expensive L-fucose.



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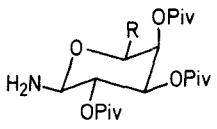
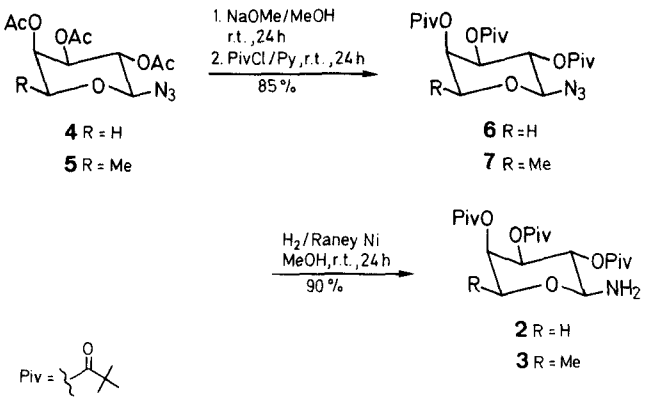


2 R = H
3 R = Me

Unlike the *O*-pivaloyl-galactosylamine **1**, the arabinosylamine cannot be obtained from the perpivaloylated arabinopyranose via tin tetrachloride catalyzed reaction with trimethylsilyl azide. Under these conditions, *O*-pivaloyl-arabinofuranosyl azides and the undesired α-anomeric pyranosyl azide are the prevailing products. In this case, the reported *trans* selectivity of this process[9] is not observed. Therefore, the peracetylated arabinopyranose is transformed to 2,3,4-tri-*O*-acetyl-α-arabinopyranosyl azide (**4**), as has been described by Paulsen and co-workers.[9] After deacetylation and subsequent pivaloylation, **4** delivers the desired 2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosyl azide (**6**). It is finally reduced by hydrogenation with Raney nickel to furnish the auxiliary **2**.

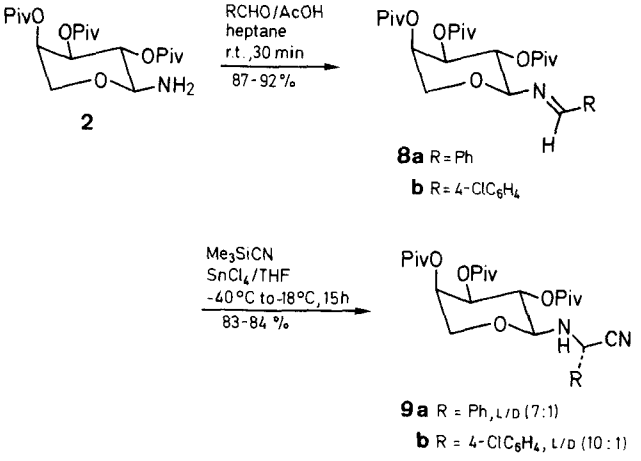
It appeared that the analogous synthetic scheme is also efficient for the synthesis of the *O*-pivaloylated fucosylamine **3**. The formation of the *O*-acetyl-pyranosyl azides **4, 5**, their deacetylation and subsequent pivaloylation to give **6** or **7**, respectively, proceed with overall yields of 85%. The hydrogenolysis runs with a yield of more than 90%.



4 R = H
5 R = Me
6 R = H
7 R = Me
2 R = H
3 R = Me

Scheme 1

To obtain L-amino nitriles via Strecker syntheses, the arabinosylamine **2** is condensed with aldehydes to give the *N*-arabinosylimines **8** which with trimethylsilyl cyanide/tin tetrachloride furnish the α-amino nitriles **9**. The diastereoselectivity determined by analytical HPLC directly from the hydrolyzed reaction mixture amounts to 7–10:1 in favor of the L-diastereomer **L-9**.

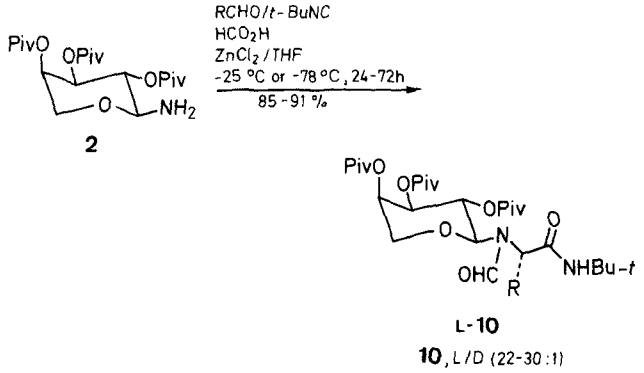


2
8a R = Ph
b R = 4-ClC$_6$H$_4$
9a R = Ph, L/D (7:1)
b R = 4-ClC$_6$H$_4$, L/D (10:1)

Scheme 2

Recrystallization of the crude products from heptane delivers the diastereomerically pure L-amino nitriles with 83–84% yield. Hydrolysis of a sample of pure **L-9a** with hydrogen chloride/formic acid[4] exclusively forms L-phenylglycine, according to TLC of the obtained product on a "chiral plate".[10]

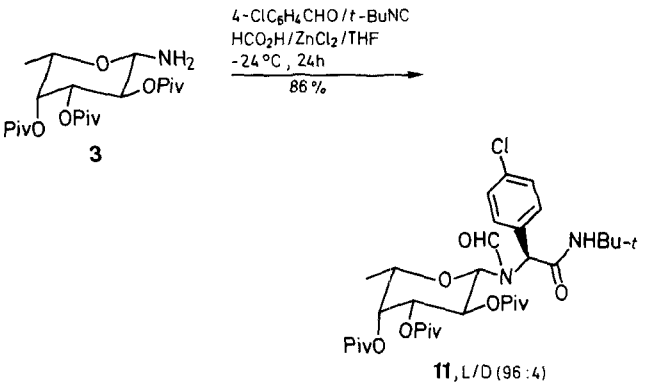
The arabinosylamine **2** applied in Ugi four-component[11] reactions shows a slightly enhanced reactivity in comparison to the galactosylamine. At −25 °C, in the cases of reactive aliphatic aldehydes at −78 °C, **2** reacts with aldehydes, *tert*-butyl isocyanide and formic acid in the presence of zinc chloride in tetrahydrofuran to form the *N*-formyl-*N*-arabinosyl amino acid amides **10** in almost quantitative yield.[8] The diastereoselectivity achieved is high leading to a preferred formation of the L-amino acid diastereomers **L-10** of 22:1 to 30:1.



Scheme 3

Pure L-amino acid diastereomers **L-10** are isolated in high yield (Table 1) by simple purification procedures. The aromatic compounds **10c–e** can be purified either by crystallization from heptane or by flash-chromatography whereas the phenylalanine derivative **10a** favorably is purified by flash-chromatography. The *tert*-leucin derivative **10b** has to be crystallized from methanol/water.

The L-fucopyranosylamine **3** is a likewise efficient stereodifferentiating auxiliary in the Ugi reaction. With 4-chlorobenzaldehyde, *tert*-butyl isocyanide, formic acid and zinc chloride the *N*-fucosyl-(4-chlorophenyl)glycine derivative **11** is obtained with diastereoselectivity of 24:1 in favor of the L-diastereomer. Recrystallization from dichloromethane/heptane gives pure **L-11**.



Scheme 4

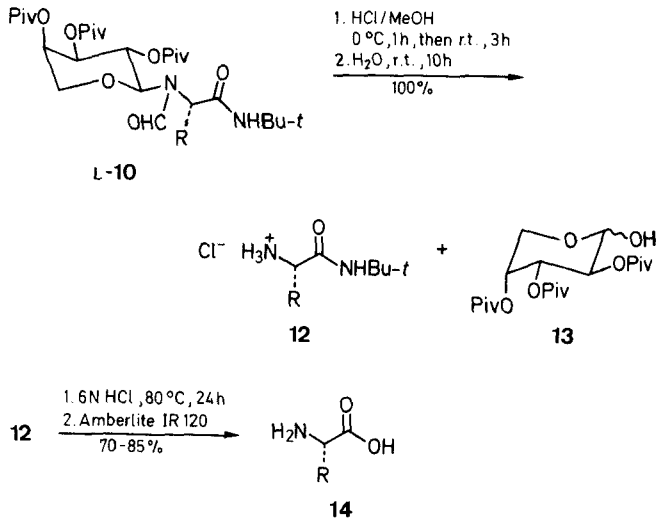
The free enantiomerically pure L-amino acids can easily be released from the carbohydrate templates by a two-step acidic hydrolysis. Treatment of the *N*-arabinosyl derivatives **10** with hydrogen chloride/methanol results in the removal of the formyl group. Subsequent addition of water causes the smooth and quantitative cleavage of the *N*-glycosidic bond. Extraction of the obtained aqueous solution of the L-amino acid amide hydrochlorides **12** with pentane permits the quantitative recover of the carbohydrate template 2,3,4-tri-*O*-pivaloyl-D-arabinose **13**. Hydrolysis of the amides **12** is achieved with 6N hydrogen chloride at 80 °C and subsequent deprotonation with ion exchange resin delivers the free L-amino acids **14** (see Table 2).

Comparison of the optical rotation values of the synthesized L-amino acids with those reported in the literature (see Table 2) reveals that only the thienyl compounds **14d** partly racemizes (~10%) under the con-

Table 1. Diastereoselective Ugi Synthesis of *N*-Arabinosyl Amino Acid Amides **10** Using Tri-*O*-pivaloyl-α-D-arabinopyranosylamine (**2**)

Product	R	Temp./Time (°C)/h	Kinetic Ratio[a] 2L/2D	Yield of L-**10** (%)	mp. (°C)	$[\alpha]_D^{20}$ ($c = 1$, MeOH)	Molecular Formula[b]	^{1}H-NMR ($CDCl_3$/TMS) δ 1-H(d)[c]	α-CH(s)
10a	Bn	−78/24	97:3	87[d]	amorphous	−2.6[e]	$C_{34}H_{52}N_2O_9$ (632.8)	5.87* 5.90	3.90*[f] 4.52
10b	*t*-Bu	−25/72	97:3	85[h]	235	−20.4[e]	$C_{31}H_{54}N_2O_9$ (598.8)	6.00* 5.90	4.0–3.5[i] –
10c	4-ClC_6H_4	−25/24	98:2	91[j]	202	+36.8	$C_{33}H_{49}ClN_2O_9$ (653.2)	5.17* 5.99	5.01* 5.11
10d	2-furyl	−25/24	96:4	85[d]	146	+9.9	$C_{31}H_{48}N_2O_{10}$ (608.7)	5.80* 4.99	5.09* 5.58
10e	2-thienyl	−25/24	96:4	85[j]	163	+13.5	$C_{31}H_{48}N_2O_9S$ (624.8)	5.80* 4.96	5.21* 5.51

[a] HPLC on 120-5 μ C18 in MeOH/20% H_2O.
[b] Satisfactory elemental analysis obtained: C ±0.1, H ±0.15, N ±0.1.
[c] $J_{1,2} = 9.4$–9.6 Hz.
[d] Purified by flash-chromatography, light petroleum ether/EtOAc (5:1).
[e] $c = 2$.
[f] dd ($J_a = 5.3$ Hz, $J_b = 10.5$ Hz).
[g] Not detectable.
[h] Recrystallized from MeOH/H_2O.
[i] (m, 3H, 5-H, 5'-H, α-CH).
[j] Recrystallized from heptane.
* Major rotamer.



Scheme 5

Table 2. Two-Step Hydrolysis of *N*-Arabinosyl Amino Acid Amides **10** and Synthesis of L-Amino Acids **14**

Product	R	Overall Yield (%)	$[\alpha]_D^{20}$ [Lit. $[\alpha]_D$]
14a	*t*-Bu	70	+8.5 (*c* = 2, 1.5N HCl), [$[\alpha]_D^{20}$ +9.0 (*c* = 3, 5N HCl)][13]
14b	Bn	82	−33.3 (*c* = 0.5, H_2O), [$[\alpha]_D^{25}$ −34.8 (*c* = 1, H_2O)][14]
14c	4-ClC_6H_4	85	+139.5 (*c* = 1, 1N HCl), [$[\alpha]_D^{20}$* −138.7 (*c* = 1, 1N HCl)][15]
14d	2-thienyl	80	+58.1 (*c* = 0.5, H_2O), [$[\alpha]_D^{23}$ +73.4 (*d* = 1, H_2O)]

[a] (*R*)-Enantiomer.

ditions applied. The other amino compounds are isolated as pure L-enantiomers.

In conclusion, the D-arabinosylamine **2** and the L-fucosylamine **3** are efficient stereodifferentiating templates in the synthesis of enantiomerically pure L-amino acids according to the Strecker or the Ugi methodology. They are fortunately complementary to the galactosylamine which is the efficient auxiliary for the synthesis of D-amino acids.[6]

TLC was performed on Silica Gel 60 F_{254} (E. Merck, Darmstadt, Germany), detection with UV light (λ = 254 nm) and with 0.2% 3-methoxyphenol/2N H_2SO_4; amino acid compounds were detected with 0.3% ninhydrine in methanolic AcOH (3%). Flash-chromatography was carried out on silica gel MN 60 (0.04–0.063 mm), Macherey and Nagel, Düren, Germany. For TLC of amino acids "chiral plate",[10] Macherey and Nagel was used. Analytical HPLC was performed with a LKB 2150 equipment including a LKB 2140 Rapid Spectral Detektor (diode-array-detection 190–370 nm), using Nucleosil 120-5 μ C-18, reversed phase. 400 MHz ^{1}H- and 100.6 MHz ^{13}C-NMR spectra were recorded on a Bruker AM-400 in $CDCl_3$ with TMS as internal standard. Optical rotations were measured with a Perkin Elmer 241 polarimeter.

2,3,4-Tri-*O*-acetyl-β-L-fucopyranosyl Azide (5):
To 1,2,3,4-Tetra-*O*-acetyl-α,β-L-fucopyranose[12] (0.15 mol) dissolved in CH_2Cl_2 (350 mL), Me_3SiN_3 (22.5 mL) and, subsequently, $SnCl_4$ (3 mL) are added. After 3 h at r.t. the mixture is extracted with H_2O (3 × 100 mL), sat. aq $NaHCO_3$ (3 × 100 mL) and again with H_2O (100 mL), dried ($MgSO_4$) and evaporated in vacuo to give **5**; yield: 78%; mp 106 °C; $[\alpha]_D^{20}$ + 20.9° (*c* = 1, $CHCl_3$).

$C_{12}H_{16}N_3O_7$ calc. C 45.86 H 5.13 N 13.31
(314.3) found 45.66 5.18 13.37

^{1}H-NMR ($CDCl_3$/TMS): δ = 4.55 (d, 1 H, $J_{1,2}$ = 8.7 Hz, 1-H), 5.00 (dd, 1 H, $J_{2,3}$ = 10.3 Hz, 3-H), 5.11 (dd, 1 H, 2-H), 5.23 (m, 1 H, $J_{3,4}$ = 3.4 Hz, 4-H).

^{13}C-NMR ($CDCl_3$/TMS): δ = 15.94 (CH_3), 68.23, 69.94, 71.13, 71.52 (C-2–C-5), 88.16 (C-1).

α-D-Arabinopyranosyl Azide and β-L-Fucopyranosyl Azide:
To a solution of 2,3,4-tri-*O*-acetyl-α-D-arabinopyranosyl azide[9] (**4**; 0.1 mol) or 2,3,4-tri-*O*-acetyl-β-L-fucopyranosyl azide (**5**; 90 mmol), in MeOH (200 mL), 1N NaOMe in MeOH (1 mL) is added. After 2 h, the solution is neutralized using ion exchange resin IR 200 (H^+ form, 3 g), filtered and the solvent is evaporated in vacuo.

α-D-Arabinopyranosyl Azide: yield: 100%; mp 93 °C; $[\alpha]_D^{22}$ − 21.2° (*c* = 1, H_2O).

$C_5H_9N_3O_4$ calc. C 34.29 H 5.18 N 23.99
(175.1) found 34.20 5.17 23.95

^{13}C-NMR ($CDCl_3$/DMSO-d_6/TMS): δ = 67.66, 67.85, 70.20, 72.50 (C-2–C-5), 90.65 (C-1).

β-L-Fucopyranosyl Azide: yield: 100%; mp 84 °C; $[\alpha]_D^{20}$ + 24.9° (*c* = 1, MeOH).

$C_6H_{11}N_3O_4$ calc. C 38.08 H 5.86 N 22.22
(189.2) found 38.07 5.94 22.18

^{13}C-NMR (DMSO-d_6/TMS): δ = 16.46 (CH_3), 69.93, 70.84, 72.42, 73.41 (C-2–C-5), 90.44 (C-1).

2,3,4-Tri-*O*-pivaloyl-glycosyl Azides 6, 7:
To a solution of the α-D-arabinopyranosyl azide (0.1 mol) or of the β-L-fucopyranosyl azide (0.1 mol), respectively, in pyridine (150 mL) at 0 °C, pivalolyl chloride (40 mL) is added dropwise. After 24 h at r.t. pyridine and pivaloyl chloride are evaporated in vacuo, the residue dissolved in CH_2Cl_2 (200 mL), is washed with 2N HCl (100 mL), sat. aq $NaHCO_3$ (5 × 50 mL) and H_2O (100 mL), dried ($MgSO_4$) and concentrated in vacuo. Recrystallization from MeOH delivers pure compounds:

2,3,4-Tri-O-pivaloyl-α-D-arabinopyranosyl Azide (**6**): yield: 89%; mp 90 °C; $[\alpha]_D^{22}$ + 0.93° (*c* = 1, $CHCl_3$).

$C_{20}H_{33}N_3O_7$ calc. C 56.19 H 7.78 N 9.83
(427.5) found 56.15 7.77 9.92

^{1}H-NMR ($CDCl_3$/TMS): δ = 4.54 (d, 1 H, $J_{1,2}$ = 9.7 Hz, 1-H), 5.08 (dd, 1 H, $J_{3,4}$ = 3.3 Hz, 3-H), 5.19 (dd, 1 H, 2-H), 5.23 (m, 1 H, 4-H).

2,3,4-Tri-O-pivaloyl-β-L-fucopyranosyl Azide (**7**): yield: 84%; mp 80 °C; $[\alpha]_D^{22}$ − 17.1° (*c* = 1.2, $CHCl_3$).

$C_{21}H_{35}N_3O_7$ calc. C 57.13 H 7.99 N 9.52
(441.5) found 57.12 8.01 9.54

^{1}H-NMR ($CDCl_3$/TMS): δ = 4.54 (d, 1 H, $J_{1,2}$ = 8.6 Hz, 1-H), 5.07 (dd, 1 H, $J_{3,2}$ = 10.4 Hz, 3-H), 5.16 (dd, 1 H, 2-H), 5.23 (m, 1 H, $J_{3,4}$ = 3.1 Hz, 4-H).

Tri-*O*-pivaloyl-glycosylamines 2, 3:
A solution of the *O*-pivaloylated glycosyl azide **6** or **7**, respectively, (0.1 mol) in MeOH (250 mL, containing 1–5% of CH_2Cl_2) is hydrogenated under atmospheric pressure in the presence of Raney Ni (10 g). After 3 h (TLC control) the catalyst is removed by centrifugation, the solvent is evaporated in vacuo and the remaining residue is recrystallized from MeOH.

2,3,4-Tri-O-pivaloyl-α-D-arabinopyranosylamine (**2**): yield: 88%; mp 106 °C; $[\alpha]_D^{22}$ − 46.7° (*c* = 1, $CHCl_3$).

$C_{20}H_{35}NO_7$ calc. C 59.83 H 8.79 N 3.49
(401.5) found 59.72 8.81 3.29

^{1}H-NMR ($CDCl_3$/TMS): δ = 4.02 (d, 1 H, $J_{1,2}$ = 8.4 Hz, 1-H), 5.01 (dd, 1 H, 2-H), 5.07 (dd, 1 H, $J_{3,2}$ = 10.2 Hz, $J_{3,4}$ = 3.3 Hz; 3-H), 5.18 (m, 1 H, 4-H).

2,3,4-Tri-O-pivaloyl-β-L-fucopyranosylamine **(3)**: yield: 91%; mp 52°C; $[\alpha]_D^{22}$ −20.5° (*c* = 1, $CHCl_3$).

$C_{21}H_{37}NO_7$	calc.	C 60.70	H 8.97	N 3.37
(415.2)	found	60.66	8.87	3.31

^{1}H-NMR ($CDCl_3$/TMS): δ = 4.10 (d, 1 H, $J_{1,2}$ = 8.7 Hz, 1-H), 4.97 (dd, 1 H, 2-H), 5.09 (dd, 1 H, $J_{3,2}$ = 10.3 Hz, $J_{3,4}$ = 3.3 Hz, 3-H), 5.21 (m, 1 H, 4-H).

N-Benzylidene-2,3,4-tri-O-pivaloyl-α-D-arabinopyranosylamines 8:
To a solution of the arabinosylamine **2** (20 mmol) in heptane (30 mL), the corresponding aldehyde (30 mmol) and 30 drops of AcOH are added. After 30 min the separated H_2O is trapped by addition of Na_2SO_4 (2 g). The mixture is filtered. On cooling of the filtrate to 0°C, the aldimine **8** crystallizes. It is collected by filtration and rapidly washed with a small amount of pentane.

N-Benzylidene-2,3,4-tri-O-pivaloyl-α-arabinopyranosylamine **(8a)**: yield: 87%; mp 149°C; $[\alpha]_D^{22}$ +4.7° (*c* = 1, $CHCl_3$).

$C_{27}H_{39}NO_7$	calc.	C 66.24	H 8.03	N 2.86
(489.6)	found	66.08	8.16	2.70

^{13}C-NMR ($CDCl_3$/TMS): δ = 94.50 (C-1), 161.56 (C=N).

N-(4-Chlorobenzylidene)-2,3,4-tri-O-pivaloyl-α-D-arabinopyranosylamine **(8b)**: yield: 92%; mp 178°C; $[\alpha]_D^{22}$ +6.9° (*c* = 1, $CHCl_3$).

$C_{27}H_{38}ClNO_7$	calc.	C 61.88	H 7.31	N 2.67
(524.1)	found	61.88	7.39	2.59

^{13}C-NMR ($CDCl_3$/TMS): δ = 93.48 (C-1), 159.90 (C=N).

N-(2,3,4-Tri-O-pivaloyl-α-D-arabinopyranosyl)-L-amino Nitriles 9:
To a solution of Me_3SiCN (2.4 g, 20 mmol) and $SnCl_4$ (20 mmol) in THF (200 mL) at −40°C, a solution of the imine **8** (15 mmol) in THF (10 mL) is added within 5 min. After 15 h at −18°C, the solvent is evaporated. The residue dissolved in CH_2Cl_2 (200 mL) is extracted with 2N HCl (100 mL), sat. aq $NaHCO_3$ (3 × 100 mL) and with H_2O, dried ($MgSO_4$) and concentrated in vacuo. The remaining residue is investigated by HPLC and, finally recrystallized from heptane to give the pure L-amino nitriles **L-9**.

N-(2,3,4-Tri-O-pivaloyl-α-D-arabinopyranosyl)-L-phenylglycinonitrile **(L-9a)**: yield: 83%; mp 168°C; $[\alpha]_D^{22}$ −51.0° (*c* = 1, $CHCl_3$).

$C_{28}H_{40}N_2O_7$	calc.	C 65.10	H 7.80	N 5.42
(516.6)	found	64.94	7.82	5.42

^{13}C-NMR ($CDCl_3$/TMS): δ = 50.24 (α-C), 87.43 (C-1), 119.43 (C≡N).

N-(2,3,4-Tri-O-pivaloyl-α-D-arabinopyranosyl)-L-(4-chlorophenyl)glycinonitrile **(L-9b)**: yield: 84%; mp 178°C; $[\alpha]_D^{22}$ −47.1 (*c* = 1, $CHCl_3$).

$C_{28}H_{39}ClN_2O_7$	calc.	C 61.03	H 7.13	N 5.08
(551.1)	found	60.87	7.03	5.19

^{13}C-NMR ($CDCl_3$/TMS): δ = 49.64 (α-C), 87.47 (C-1), 119.01 (C≡N).

N-Formyl-N-glycosyl Amino Acid *N'-tert*-Butylamides 10, 11; General Procedure:
To a solution of the glycosylamine **2** or **3**, respectively, (4 mmol), the corresponding aldehyde (4.1 mmol), formic acid (4.4 mmol) and *t*-BuNC (4.2 mmol) in THF (30 mL), cooled to −25°C (for **10a** −78°C), $ZnCl_2$ (4 mmol, as 2.2 molar solution of the Et_2O complex in CH_2Cl_2) is added. The reaction is monitored by TLC (light petroleum ether/EtOAc). After complete disappearance of **2**, **3**, the solvent is evaporated in vacuo, the residue dissolved in CH_2Cl_2 (50 mL) is extracted with sat. aq $NaHCO_3$ (2 × 100 mL) and with H_2O and dried ($MgSO_4$). The solvent is evaporated in vacuo. The crude mixture of diastereomers obtained almost quantitatively is investigated by HPLC (see Table 1). Recrystallization or flash-chromatography delivers the pure *N*-formyl-*N*-(2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosyl)-L-amino acid *N'-tert*-butylamides **10** in high yield (Results and characterization, see, Table 1). From the fucosylamine, *N*-formyl-*N*-(2,3,4-tri-*O*-pivaolyl-β-L-fucopyranosyl)-L-(4-chlorophenyl)glycine *N'-tert*-butylamide **(L-11)** is obtained: Ratio of diastereomers (HPLC) (L/D) = 96:4; yield; 86% (recrystallized from heptane); mp 226°C; $[\alpha]_D^{22}$ +52.9° (*c* = 1, $CHCl_3$).

$C_{34}H_{51}ClN_2O_9$	calc.	C 61.18	H 7.65	N 4.19
(666.8)	found	61.44	7.59	4.21

^{1}H-NMR ($CDCl_3$/TMS): δ = 5.46, 5.50* (s, 1 H, α-CH), 5.85* (d, 1 H, $J_{1,2}$ = 8.9 Hz, 1-H), 8.14*, 8.36 (s, 1 H, CHO), (*: Major rotamer).

Hydrolysis of *N*-Glycosyl-L-amino Acid Amides L-10; General Procedure:
A sat. solution of HCl in MeOH (3 mL) is added to the *N*-glycosyl-L-amino acid amides **L-10** (2 mmol) dissolved in dry MeOH (10 mL). The mixture is stirred 1 h at 0°C and 3 h at r.t. H_2O (2 mL) is added and the mixture stirred for 10 h. After evaporation of the solvent, the residue is dissolved in H_2O (25 mL). The solution is extracted with pentane (2 × 20 mL). From the dried pentane solution, tri-*O*-pivaloyl-D-arabinopyranose **(13)** is recovered almost quantitatively (> 96%). The aqueous solution is evaporated to dryness to give the amino acid amides **12** quantitatively. They are heated in 6N HCl at 80°C for 24 h. The solution is evaporated to dryness and, toluene (2 × 10 mL) is destilled off from the residue, which is then dissolved in H_2O and loaded on an ion exchange column (Amberlite IR 200). After the resin has been washed to neutral reaction of the eluent, the amino acids are eluated with aq NH_4OH (3%). Evaporation of the ammonium salt solution in vacuo gives the L-amino acids **14** in crystalline form (see, Table 2).

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